Complete Summary

GUIDELINE TITLE

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2008 Jan 29. 128 p. [419 references]

GUIDELINE STATUS

This is the current release of the guideline. It was last updated on January 29, 2008.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are summarized and highlighted on the AIDSinfo Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to aidsinfowebmaster@aidsinfo.nih.gov.

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 24, 2008, Ziagen (abacavir sulfate): The U.S. Food and Drug Administration (FDA) has notified the maker of abacavir and abacavir-containing medications of the need to add information to the current BOXED WARNING about the recommendation to test all patients for the HLA-B*5701 allele before starting or restarting therapy with abacavir or abacavir-containing medications.

- March 12, 2008, Prezista (darunavir): The U.S. Food and Drug Administration (FDA) and Tibotec Therapeutics notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Prezista (darunavir) tablets regarding the risk of hepatotoxicity, specifically, drug induced hepatitis in patients receiving combination therapy with Prezista/ritonavir.
- September 10, 2007, Viracept (nelfinavir mesylate): Pfizer issued a Dear Healthcare Professional Letter to inform healthcare professionals of the presence of ethyl methanesulfonate (EMS), a process-related impurity in Viracept and to provide guidance on the use of Viracept in pregnant women and pediatric patients.
- August 16, 2007, Baraclude (Entecavir): Revisions to the prescribing information for Baraclude to indicate that the drug is not recommended for HIV/hepatitis B virus (HBV) co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) due to the potential for the development of HIV resistance.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infections (including asymptomatic, established, and acute HIV)
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology

Pediatrics
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To update the December 2007 guidelines
- To outline current understanding of how clinicians should use antiretroviral drugs to treat adults and adolescents with human immunodeficiency virus (HIV) infection in the United States

TARGET POPULATION

Adults and adolescents infected with human immunodeficiency virus (HIV)

These guidelines focus on treatment for adults and adolescents. Separate guidelines outline how to use antiretroviral therapy for such populations as pregnant women, pediatric patients, and health care workers with possible occupational exposure to HIV. There is a brief discussion of the management of women in reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise outlined by panels that have developed these guidelines.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Baseline evaluation
    - Medical history, physical examination
    - Laboratory tests, including human immunodeficiency virus antibody, CD4 cell count, plasma HIV ribonucleic acid (RNA), and other tests, as indicated
2. Initial assessment and monitoring for therapeutic response
    - CD4 counts
    - Viral load
    - Drug resistance testing
    - HLA-B*5701 screening
    - Coreceptor tropism assays
3. Initial regimens for the antiretroviral-naïve patient
    - Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen (1 NNRTI + 2 nucleoside reverse transcriptase inhibitors [NRTI])
    - Protease inhibitor (PI)-based regimen (ritonavir-boosted or unboosted PIs + 2 NRTIs)
        - Alternative PI-based regimen
    - Dual nucleoside options as part of initial combination therapy
4. Managing treatment-experienced patients
    - Assessment of treatment failure
    - Changing antiretroviral therapy
    - Therapeutic drug monitoring

- Discontinuation or interruption of antiretroviral therapy

5. Considerations for antiretroviral use in special populations
    - Acute HIV infection
    - HIV-infected adolescents
    - Injection drug users
    - HIV-infected women of reproductive age and pregnant women
    - Patients with co-infections (hepatitis B, hepatitis C, *Mycobacterium tuberculosis*)
6. Prevention counseling

MAJOR OUTCOMES CONSIDERED

- Viral load
- Immunologic function
- Adherence to treatment
- Therapy-associated adverse effects
- Quality of life
- Human immunodeficiency virus (HIV)-related morbidity and mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Data Used for Making Recommendations

In its deliberations for the guidelines, the Panel on Clinical Practices for Treatment of HIV Infection reviewed clinical trial data published in peer-reviewed journals and data prepared by manufacturers for U.S. Food and Drug Administration (FDA) review. In selected cases, data presented in abstract format in major scientific meetings were also reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Categories reflecting the quality of evidence supporting the recommendations:

I. At least one randomized trial with clinical results
II. Clinical trials with laboratory results
III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel), a working group of the Office of AIDS Research Advisory Council, develops these guidelines, which outline current understanding of how clinicians should use antiretroviral drugs to treat adults and adolescents with human immunodeficiency virus (HIV) infection in the United States. The Panel considers new evidence and adjusts recommendations accordingly. The primary areas of attention and revision have included when to initiate therapy, which drug combinations are preferred and which drugs or combinations should be avoided, and means to continue clinical benefit in the face of antiretroviral drug resistance. In contrast, some aspects of therapy, such as medication adherence, although important, have seen less rapid data evolution and thus fewer changes. Yet other topics, such as the treatment of HIV during pregnancy, have warranted more in-depth attention by separate guidelines groups.

Updating of Guidelines

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

A. Strong
B. Moderate
C. Optional
D. Should usually not be offered
E. Should never be offered

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

All revisions are summarized and highlighted on the *AIDSinfo* Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the guideline panel prior to finalization.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations usually are followed by levels of evidence (I-III) identifying the type of supporting evidence and strength of recommendation grades (A-E). Definitions for these are presented at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC) and the Department of Health and Human Services*: These guidelines were updated by the developer on January 29, 2008. Following are the major changes that have been made to the December 1, 2007, version of the guidelines, followed by the guideline recommendations. Please refer to the original guideline document at the AIDSinfo Web site for further details*.

What's New in the Document?

The following changes have been made to several sections of the December 1, 2007 version of the guidelines:

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient?

The Panel revised its recommendations for several "preferred" and "alternative" antiretroviral components for treatment-naïve patients:

- "Abacavir + lamivudine" has been changed from "alternative" to "preferred" 2-nucleoside reverse transcriptase inhibitor (NRTI) component in patients who have tested negative for HLA-B*5701 **(AII)**.
- "Zidovudine + lamivudine" has been changed from "preferred" to "alternative" 2-NRTI component **(BII)**.
- "Ritonavir-boosted saquinavir" has been changed from a protease inhibitor (PI)-option that was considered as "Acceptable as initial antiretroviral

components but inferior to preferred or alternative components" to an "alternative" PI component **(BII)**.
- The following options are no longer recommended as components for initial therapy in treatment-naïve patients:
    - Nelfinavir as PI component
    - Stavudine + lamivudine as 2-NRTI components
    - Abacavir + zidovudine + lamivudine as a triple-NRTI combination regimen

A new topic entitled "Other Treatment Options Under Investigation: Insufficient Data to Recommend" has been added, which includes a review of recent clinical trial data in treatment-naïve patients for ritonavir-boosted darunavir-based regimens, maraviroc-based regimens, and raltegravir-based regimens.

Treatment Interruption

This section has been updated with recent data on short-term and long-term treatment interruption. The Panel reaffirms their recommendation that aside from unplanned or planned short-term interruption due to illnesses precluding oral therapy or toxicities, long-term treatment interruption is not recommended unless in the context of a clinical trial **(DI)**.

Acute Human Immunodeficiency Virus (HIV) Infection

- A new table on "Identifying, diagnosing, and managing acute HIV-1 infection" has replaced the table on "Associated signs and symptoms of acute retroviral syndrome and percentage of expected frequency".
- The Panel also recommends that since clinically significant resistance to PIs is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral-naïve persons who harbor drug resistant virus, if therapy is initiated before drug resistance test results are available, consideration should be given to using a PI-based regimen **(BIII)**.

Mycobacterium Tuberculosis Disease or Latent Tuberculosis Infection with HIV Coinfection

This section has been updated with the following information:

- Discussions and recommendations on the timing of initiation of antiretroviral therapy in patients with active tuberculosis (TB), with emphasis on the risks and benefits of concomitant therapy related to overlapping toxicities, drug interactions, CD4 cell counts, and potential for immune reconstitution inflammatory syndrome.
- Recommendation for repeat testing to detect latent TB infection in persons who had CD4 count <200 cells/mm^3 and have tested negative prior to antiretroviral therapy and have improved CD4 count to >200 cells/mm^3 **(BII)**.

Table Updates

- Various tables have been updated to include information regarding etravirine, updates on various antiretroviral drugs, as well as new atazanavir dosing recommendations when used in combination with proton pump inhibitors or H2 receptor antagonists.
- The following tables have been removed from the document:
    - "Antiretroviral components that are acceptable as initial antiretroviral components but are inferior to preferred or alternative components"
    - "Treatment outcome of selected clinical trials of combination antiretroviral regimens in treatment-naïve patients with 48-week follow-up data"

Baseline Evaluation

Each patient initially entering care should have a complete medical history, physical examination, and laboratory evaluation. The purpose is to confirm the presence of HIV infection, determine if HIV infection is acute (see "Acute HIV infection" section, below), determine the presence of co-infections, and assess overall health condition as recommended by the primary care guidelines for the management of HIV-infected patients.

The following laboratory tests should be performed for each new patient during initial patient visits:

- HIV antibody testing (if laboratory confirmation not available) **(AI)**
- CD4 T-cell count **(AI)**
- Plasma HIV ribonucleic acid (RNA) **(AI)**
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN) and creatinine, urinalysis, Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) testing, tuberculin skin test (TST) or interferon-gamma release assay (IGRA) (unless a history of prior tuberculosis or positive TST or IGRA), *Toxoplasma gondii* immunoglobulin G (IgG), Hepatitis A, B, and C serologies, and Pap smear in women **(AIII)**
- Fasting blood glucose and serum lipids if considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**; and
- For patients with pretreatment HIV RNA >1,000 copies/mL, genotypic resistance testing is recommended when the patients enter into care, regardless of whether therapy will be initiated immediately **(AIII)**. If therapy is to be deferred, repeat testing at the time of antiretroviral initiation should be considered. **(CIII)** (See below under "Drug Resistance Testing.")

In addition:

- An optional test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in order to identify high risk behavior and the need for sexually transmitted disease (STD) therapy **(BII)**; and
- Chest x-ray if clinically indicated **(BIII)**

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues. Thus, the evaluation should also include assessment of substance abuse, economic factors, social support, mental illness, comorbidities,

and other factors that are known to impair the ability to adhere to treatment and to alter outcomes. Once evaluated, these factors should be managed accordingly.

Laboratory Testing for Initial Assessment and Monitoring for Treatment Responses

CD4 T-Cell Count

Use of CD4 T-Cell Count for Initial Assessment

The CD4 T-cell count is usually the most important consideration in decisions to initiate antiretroviral therapy. All patients should have a baseline CD4 cell count at entry into care **(AI)**; many authorities recommend two baseline measurements before decisions are made to initiate antiretroviral therapy because of wide variations in results **(CIII)**. The test should be repeated yet a third time if discordant results are seen **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 cell count are found below in the "When to Treat: Indications for Antiretroviral Therapy" section.

Use of CD4 T-Cell Count for Monitoring Therapeutic Response

Adequate viral suppression for most patients on therapy is defined as an increase in CD4 cell count that averages 100 to 150 cells/mm^3 per year with an accelerated response in the first three months. This is largely because of redistribution. Subsequent increases with good virologic control show an average increase of approximately 100 cells/mm^3 per year for the subsequent few years until a threshold is reached.

Frequency of CD4 T-Cell Count Monitoring

In general, CD4 count should be determined every three to six months to (1) determine when to start antiretroviral in patients who do not meet the criteria for initiation; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiating chemoprophylaxis for opportunistic infections.

Viral Load Testing

Plasma HIV RNA (viral load) may be a consideration in the decision to initiate therapy. In addition, viral load is critical for evaluating response to therapy **(AI)**. Three HIV viral load assays have been approved by the U.S. Food and Drug Administration (FDA) for clinical use:

- HIV-1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic)
- Nucleic acid amplification test for HIV RNA (NucliSens HIV-1 QT, bioMerieux); and
- Signal amplification nucleic acid probe assay (VERSANT HIV-1RNA 3.0 assay, Bayer)

One key goal of therapy is a viral load below the limits of detection (at <50 copies/mL for the Amplicor assay, <75 copies/mL for the VERSANT assay, and

<80 copies/mL for the NucliSens assay). This goal should be achieved by 16 to 24 weeks **(AI)**. Recommendations for the frequency of viral load monitoring are summarized below and in Table 2 of the original guideline document.

At Initiation or Change in Therapy

Plasma viral load should be measured immediately before treatment and at 2 to 8 weeks after treatment initiation or treatment changes because of suboptimal viral suppression. In the latter measure, there should be a decrease of at least a 1.0 $\log_{10}$ copies/mL **(BI)**.

In Patients With Viral Suppression Where Changes are Motivated by Drug Toxicity or Regimen Simplification

Some experts also recommend repeating viral load measurement within 2 to 8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BII)**.

In Patients on a Stable Antiretroviral Regimen

The viral load testing should be repeated every 3 to 4 months thereafter or if clinically indicated **(BII)**. (See Table 2 in the original guideline document.)

Monitoring Patients with Suboptimal Response

In addition to viral load monitoring, a number of additional factors should be assessed, such as non-adherence, altered pharmacology, or drug interactions. Resistance testing may be helpful in identifying the presence of resistance mutations that may necessitate a change in therapy **(AII)**.

Drug Resistance Testing

Panel's Recommendations

- HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately **(AIII)**. If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered **(CIII)**.
- A genotypic assay is generally preferred for antiretroviral-naïve persons **(AIII)**.
- HIV drug resistance testing should be performed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure **(AII)**.
- Drug resistance testing should also be performed when managing suboptimal viral load reduction **(AII)**.
- Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy **(AII)**.
- Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable

HIV RNA levels while on therapy **(AII)**.

- Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, because amplification of the virus is unreliable **(DIII)**.

HLA-B*5701 Screening

Panel's Recommendations:

- The Panel recommends screening for HLAB*5701 before starting patients on an abacavir-containing regimen, to reduce the risk of hypersensitivity reaction **(AI)**.
- HLA-B*5701-positive patients should not be prescribed abacavir **(AI)**.
- The positive status should be recorded as an abacavir allergy in the patient's medical record **(AII)**.
- When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction **(CIII)**.

Coreceptor Tropism Assays

Panel's Recommendations

- Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered **(AII)**.
- Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor **(BIII)**.

Treatment Goals

The primary goals driving the decision to initiate antiretroviral therapy are to:

- Reduce HIV-related morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic functions
- Maximally and durably suppress viral load
- Prevent vertical HIV transmission

Strategies to Achieve Treatment Goals

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define priorities and determine treatment goals and options. See the original guideline document for more information on these topics.

- Selection of Initial Combination Regimen
- Pretreatment Drug Resistance Testing

- Improving Adherence

When to Start: Indications for Initiation of Antiretroviral Therapy

Panel's Recommendations

- Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm^3. The data supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm^3 and with a history of AIDS **(AI)** than for those with CD4 T-cell counts between 200 and 350 cells/mm^3 **(AII)**.
- Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:
    a. Pregnant women **(AI)**
    b. Patients with HIV-associated nephropathy **(AI)** and
    c. Patients coinfected with HBV when treatment for HBV infection is indicated **(BIII)**
- Antiretroviral therapy may be considered in some patients with CD4 T-cell counts >350cells/mm^3. (See original guideline document for further discussion.)
- The necessity for patient adherence to a long-term drug regimen should be discussed in depth by the patient and clinician **(AIII)**. Barriers to adherence should be addressed before therapy is initiated.

Before initiating therapy, patient counseling and education should be conducted. The patient should understand the potential benefits and risks of antiretroviral therapy, including short-and long-term adverse drug effects and the need for long-term commitment and adherence to the prescribed treatment regimen.

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Summary of Recommended Regimens

The most extensively studied combination antiretroviral regimens for treatment-naïve patients generally consist of one NNRTI with two NRTIs, or a PI (with or without ritonavir-boosting) with two NRTIs. A list of Panel-recommended components for initial therapy in treatment naïve patients can be found in Table 6 of the original guideline document. Column A lists the preferred and alternative NNRTI and PI components, and Column B lists the preferred and alterative dual-NRTI components. To construct a complete three- or four-drug antiretroviral regimen, one component should be selected from Column A and one from Column B. A list of agents or components not recommended for initial treatment can be found in Table 7 of the original guideline document. Some agents or components not generally recommended for use because of lack of potency or potential serious safety concerns are listed in Table 8 of the original guideline document. Potential advantages and disadvantages for the components recommended as initial therapy for treatment-naïve patients are listed in Table 9 of the original guideline document to guide prescribers in choosing the regimen best suited for an individual patient.

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized and should consider a number of factors including:

- Comorbidity (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, pregnancy, renal diseases, or tuberculosis)
- Patient adherence potential
- Convenience (e.g., pill burden, dosing frequency, and food and fluid considerations)
- Potential adverse drug effects
- Potential drug interactions with other medications
- Pregnancy potential
- Results of genotypic drug resistance testing
- Gender and pretreatment CD4 T-cell count if considering nevirapine
- HLA B*5701 testing if considering abacavir

NNRTI-Based Regimens (1 NNRTI + 2 NRTIs)

Panel's Recommendations

Preferred NNRTI **(AII)**:

- Efavirenz (except during first trimester of pregnancy or in women with high pregnancy potential*)

Alternative NNRTI **(BII)**:

- Nevirapine may be used as an alternative in adult females with CD4 T-cell counts <250 cells/mm^3 and adult males with CD4 T-cell counts <400 cells/mm^3

*Women of child bearing age with high pregnancy potential are those who are trying to conceive or who are sexually active with men and not using effective and consistent contraception.

PI-Based Regimens (Ritonavir-Boosted or Unboosted PIs + 2 NRTIs)

Panel's Recommendations

Preferred PIs (in alphabetical order):

- Atazanavir + ritonavir **(AIII)**
- Fosamprenavir + ritonavir twice-daily **(AII)**
- Lopinavir/ritonavir (co-formulated) twice-daily **(AII)**

Alternative PIs **(BII)** (in alphabetical order):

- Atazanavir*
- Fosamprenavir
- Fosamprenavir + ritonavir once-daily
- Lopinavir/ritonavir (co-formulated) once-daily

- Saquinavir + ritonavir

* Ritonavir 100 mg per day must be given when tenofovir or efavirenz is used with atazanavir.

Dual-Nucleoside Options as Part of Initial Combination Therapy

Panel's Recommendations

Preferred Dual-NRTI **(AII)** (in alphabetical order):

- Abacavir/lamivudine* (co-formulated)
- Tenofovir/emtricitabine* (co-formulated)

Alternative Dual-NRTI **(BII)** (in order of preference):

- Zidovudine/lamivudine* (co-formulated)
- Didanosine + (lamivudine or emtricitabine)

*Emtricitabine may be used in place of lamivudine or vice versa.

Other Treatment Options Under Investigation: Insufficient Data to Recommend

Several novel treatment regimens using agents approved for treatment-experienced patients are currently in Phase II or III clinical trials, evaluating their safety and efficacy in treatment-naïve patients. Preliminary data from these trials are summarized in the original guideline document for the following:

- Ritonavir-boosted darunavir-based regimen
- Raltegravir-based regimen
- Maraviroc-based regimen

What Not to Use: (See Table 8 in the original guideline document)

Some antiretroviral regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacological concerns. These are summarized below.

Antiretroviral Regimens Not Recommended

Monotherapy with NRTI **(EII)**

Single NRTI therapy does not demonstrate potent and sustained antiviral activity and should not be used. For prevention of mother to child transmission, zidovudine monotherapy might be considered in certain unusual circumstances. See the NGC summary: Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir or atazanavir, are under investigation but cannot be recommended outside of a clinical trial at this time.

Dual Nucleoside Regimens **(EII)**

These regimens are not recommended because they have not demonstrated potent and sustained antiviral activity as compared with three-drug combination regimens.

Triple-NRTI Regimens **(EII)**

Except for abacavir/lamivudine/zidovudine **(DII)** and possibly zidovudine/lamivudine + tenofovir **(DII)**, triple-NRTI regimens should NOT be used routinely because of suboptimal virologic activity or lack of data.

Antiretroviral Components Not Recommended (in alphabetical order) (See the original guideline document for more information on these components.)

- *Atazanavir + Indinavir* **(EIII)**
- *Didanosine + Stavudine* **(EII)**
- *Two-NNRTI* **(EII)**
- *Efavirenz in First Trimester of Pregnancy and in Women with Significant Childbearing Potential* **(EIII)**
- *Emtricitabine + Lamivudine* **(EIII)**
- *Nelfinavir in Pregnant Women* **(EIII)**
- *Nevirapine Initiated in Treatment-naïve Women with CD4 Counts >250 cells/mm^3 or in Treatment-naive Men with CD4 Counts >400 cells/mm^3* **(DI)**
- *Saquinavir., unboosted)* **(EII)**
- *Stavudine + Zidovudine* **(EII)**

Limitations to Treatment Safety and Efficacy

A number of factors may influence the safety and efficacy of antiretroviral therapy in individual patients. Examples include, but are not limited to: nonadherence to therapy, adverse drug reactions, drug-drug interactions, and development of drug resistance. Each is discussed in the original guideline document. Drug resistance, which has become a major reason for treatment failure, is discussed in greater detail in the section, "Management of the Treatment-Experienced Patient," below.

Management of the Treatment-Experienced Patient

Panel's Recommendations

- In treatment-experienced patients with suppressed viremia, assess adherence frequently and simplify the regimen as much as possible. Change individual antiretroviral drugs to reduce or manage toxicity, as needed.
- Evaluation of antiretroviral treatment failure in a patient should include an assessment of the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; HIV RNA and CD4 T-cell

count trends over time; and the results of prior drug resistance testing.

- Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated HIV RNA level >400 copies/mL after prior suppression of viremia.
- Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation) **(AI)**.
- The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, HIV RNA <50 copies/mL **(AI)**.
- Use the treatment history and the past and current resistance test results to identify fully active agents to design a new regimen **(AII)**. A fully active agent is one that is likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug resistance testing. Adding at least two, and preferably three, fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity **(BII)**.
- Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 response despite virologic suppression.
- For immunologic failure, current medications, untreated coinfection, and serious medical conditions should be assessed.
- There is no consensus for when and how to treat immunologic failure.
- Assessing and managing a patient who has antiretroviral experience, who exhibits drug resistance, and who is experiencing treatment failure is complex and expert advice is critical.

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression (see below).

Many factors are associated with an increased risk of treatment failure, including:

- Baseline patient factors such as:
    - Earlier calendar year of starting therapy, in which less potent regimens or less well-tolerated antiretroviral drugs were used
    - Higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
    - Lower pretreatment or nadir CD4 T-cell count
    - Prior AIDS diagnosis
    - Comorbidities (e.g., depression, active substance use)
    - Presence of drug-resistant virus
    - Prior treatment failure, with development of drug resistance or cross resistance
- Incomplete medication adherence and missed clinic appointments
- Drug side effects and toxicity
- Suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications)
- Suboptimal potency of the antiretroviral regimen; and/or

- Other, unknown reasons

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by:

- Reviewing the medical history including:
    - Change in HIV RNA and CD4 T-cell count over time
    - Occurrence of HIV-related clinical events
    - Antiretroviral treatment history
    - Results of prior resistance testing (if any)
    - Medication-taking behavior, including adherence to recommended drug doses, dosing frequency, and food/fasting requirements
    - Tolerability of the medications
    - Concomitant medications (with consideration for adverse drug-drug interactions)
    - Comorbidities (including substance use)
- Performing a physical examination to assess for signs of clinical progression

In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

Initial Assessment of Treatment Failure

In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure because the approaches to subsequent treatment will differ. The following assessments should be initially undertaken:

- Adherence. Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) for non-adherence (e.g., access to medications, depression, active substance use), and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) **(AIII)**. (See "Adherence" in the original guideline document).
- Medication Intolerance. Assess the patient's side effects. Address and review the likely duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance may include:
    - Using symptomatic treatment (e.g. antiemetics, antidiarrheals)
    - Changing one drug to another within the same drug class, if needed (e.g., change to tenofovir or abacavir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms) **(AII)**
    - Changing drug classes (e.g., from an NNRTI to a PI, from an injectable drug to an oral agent) if necessary **(AII)**
- Pharmacokinetic Issues. Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible **(AIII)**. (See also "Therapeutic Drug Monitoring" in the original guideline document.)

- Suspected Drug Resistance. Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation **(AII)** (see "Drug Resistance Testing" in the original guideline document).

Further Assessment of Treatment Failure

When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make an assessment for virologic failure, immunologic failure, and clinical progression.

Virologic suppression can be defined as a sustained reduction in HIV RNA level below the assay limit of detection (e.g., 50 copies/mL). Virologic failure is best understood in the context of virologic success; that is, virologic failure is defined as the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as any of the following:

- Incomplete virologic response: Two consecutive HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient who is initiating therapy. Baseline HIV RNA may affect the time course of response, and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ decrease in HIV RNA copies/mL at 1 to 4 weeks after starting therapy.
- Virologic rebound: After virologic suppression, repeated detection of HIV RNA above the assay limit of detection (e.g., 50 copies/mL).

Assessment of Virologic Failure

There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000 to 5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations and may limit future treatment options. Isolated episodes of viremia ("blips", e.g., single levels of 51 to 1,000 copies/mL) may simply represent laboratory variation and usually are not associated with subsequent virologic failure, but rebound to higher viral loads or more frequent episodes of viremia increase the risk of failure.

When assessing virologic failure, one should assess the degree of drug resistance, and should take into account prior treatment history and prior resistance test results **(AII)**. Drug resistance tends to be cumulative for a given individual; thus all prior treatment history and resistance test results should be taken into account.

Management of Virologic Failure

General Approach

Ideally, one should design a regimen with at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing or new mechanistic class **(BII)**. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens. They included lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs (e.g., NNRTI, entry inhibitor, integrase inhibitor), and using ritonavir-boosted PIs in PI-experienced patients. More recent studies show that higher CD4 T-cell counts and higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) are associated with better virologic responses.

In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance **(DII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 T-cell count $<100/mm^3$) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and or transient increases in CD4 T-cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment-experienced patient is complicated, and consultation with an expert is advised.

Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA and a decrease in the CD4 T-cell count, and it increases the risk for clinical progression. Therefore, it is not recommended **(DIII)**.

See the original guideline document for information on sequencing and cross resistance, and newer agents.

Specific clinical scenarios follow:

- Prior Treatment With No Resistance Identified. Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications?) and/or non-adherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2 to 4 weeks) to determine if a resistant strain emerges **(CIII)**. Consider intensifying with one drug (e.g., tenofovir) **(BII)** or pharmacokinetic enhancement (use of ritonavir boosting of an unboosted protease inhibitor, e.g., atazanavir, fosamprenavir) **(BII)**.
- Prior Treatment and Drug Resistance. The goals in this situation are to resuppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Discontinuing an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance in order to

decrease the risk of selecting additional NNRTI-resistance mutations is particularly important, because newer NNRTIs with activity against some NNRTI-resistant strains are available. A new regimen should include at least two, and preferably three, fully active agents **(BII)**.

- Extensive Prior Treatment and Drug Resistance. The goal is to re-suppress the HIV RNA levels maximally (e.g., to <50 copies/mL). With the availability of multiple new antiretroviral drugs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. In some cases, however, viral suppression may be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits; however, this must be balanced with the ongoing risk for accumulating additional resistance mutations.
- New Regimen That Contains at Least Two Fully Active Agents Cannot Be Identified. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, decreases the risk of disease progression. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL.

Immunologic Failure

Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T-cell counts above a specific threshold (e.g., >350 or 500 cells/mm^3) over a specific period of time (e.g., 4 to 7 years). Others have focused on an inability to increase CD4 T-cell counts above pretherapy levels by a certain threshold (e.g. >50 or 100 cells/mm^3) over a given time period. The former approach may be preferable because of recent data linking these thresholds with the risk of non-AIDS clinical events.

Factors Associated with Immunologic Failure

- CD4 count <200/mm^3 when starting ART
- Older age
- Coinfection (e.g., HCV)
- Medications, both antiretrovirals (zidovudine [ZDV], tenofovir [TDF] + didanosine [ddI]) and other medications
- Persistent immune activation
- Loss of regenerative potential of the immune system

Assessment of Immunologic Failure

CD4 T-cell count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., interferon, cancer chemotherapy, prednisone, zidovudine, combination of tenofovir and didanosine). Untreated

coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure

There is no consensus on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 T-cell counts $<200/mm^3$. Patients with higher CD4 T-cell counts have a low risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the antiretroviral drug regimen. Because ongoing viral replication occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However this strategy does not result in clear virologic or immunologic benefit. Others suggest changing the regimen (e.g., to a more suppressive regimen or from an NNRTI-based regimen to a PI-based regimen, based on some evidence that suggests improved CD4 T-cell count responses); however, these strategies have not been formally tested.

Immune-based therapies, such as interleukin-2, demonstrated robust and sustained CD4 T-cell count increases in some studies. However, controversy persists as to how much enhancement of immune function occurs. With this controversy, drug-associated side effects, and the need for parenteral administration, this strategy cannot be recommended unless with enrollment into a clinical trial **(DII)**. Other investigational immune-based therapies (e.g., growth hormone, cyclosporine, interleukin-7) have associated toxicity and costs and cannot be recommended routinely. Currently, immune-based therapies should only be used in the context of a clinical trial **(DII)**.

Clinical Progression

Clinical progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression in 2.5 years.

Management of Clinical Progression

Consider the possibility of immune reconstitution syndrome, which typically occurs within the first 3 months after starting effective antiretroviral therapy and which may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia and adequate immunologic response **(BIII)**.

Relationship Among Virologic Failure, Immunologic Failure, and Clinical Progression

Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters. In addition, virologic failure, immunologic failure, and clinical

progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years.

Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents

Therapeutic drug monitoring (TDM) is a strategy applied to certain antiarrhythmics, anticonvulsants, and antibiotics to utilize drug concentrations to design regimens that are safe and will achieve a desired therapeutic outcome. Refer to the original guideline document for a detailed discussion of this topic including:

- TDM with PIs and NNRTIs
- TDM with NRTIs
- Scenarios for Use of TDM
- Use of TDM to Monitor Drug Concentrations
- Limitations to Using TDM in Patient Management
- TDM in Different Patient Populations (e.g., patients with wild-type virus, treatment-experienced patients)

A final caveat to the use of measured drug concentration in patient management is a general one: drug concentration information cannot be used alone; it must be integrated with other clinical and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians employing a TDM strategy for patient management should consult the most current literature.

Discontinuation or Interruption of Antiretroviral Therapy

Short-term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of antiretroviral therapy vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or nonavailability of drugs. Stopping antiretroviral drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

<u>Unanticipated Need for Short-Term Interruption</u>

- **When a patient experiences a severe or life-threatening toxicity or unexpected inability to take oral medications** – all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

<u>Planned Short-Term Interruption (>2 to 3 Days)</u>

- **When all regimen components have similar half-lives and do not require food for proper absorption** -- all drugs should be stopped simultaneously or may be given with a sip of water, if allowed. All discontinued regimen components should be restarted simultaneously.

- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient is required to take nothing by mouth for a sustained period of time** -- temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the antiretroviral regimen contains drugs with differing half-lives** -- stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See "Discontinuation of efavirenz, etravirine, or nevirapine" in the original guideline document.)

Interruption of Therapy after Pregnancy

During pregnancy, HIV-infected pregnant women who otherwise do not meet current CD4 count or clinical criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. After delivery, these women may desire to stop therapy. Discontinuation recommendations are in the current guidelines for pregnant women. (See "HIV-Infected Women of Reproductive Age and Pregnant Women" below.)

Planned Long-term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. None of these approaches can be recommended at this time outside of controlled clinical trials.

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression** -- the optimal duration of treatment and the consequences of treatment discontinuation are not known at this time. (See "Acute HIV Infection" section below.)
- **In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations** -- interruption is generally not recommended unless it is done in a clinical trial setting. Several clinical trials, yielding conflicting results, have been conducted to better understand the role of treatment interruption in these patients. The largest of these studies showed negative clinical impact of treatment interruption in these patients. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit; therefore, interruption of therapy is not recommended.
- **In patients on antiretroviral therapy who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 count was either above or below that recommended threshold** -- interruption is also not recommended unless it is done in a clinical trial setting. (See the original guideline document for discussion of potential adverse outcomes seen in some treatment interruption trials.)

Planned long-term therapy interruption strategies cannot be recommended at this time outside of controlled clinical trials **(DI)** based on available data and a range of ongoing concerns (see below).

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, increased risk for HIV transmission, decline of CD4 cell count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include

- **Discontinuation of efavirenz, etravirine, or nevirapine**. The optimal interval between stopping efavirenz, etravirine, or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of these drugs after discontinuation ranges from less than one week to more than three weeks. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphism may be more common among specific ethnic groups, such as African Americans and Hispanics. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine plus lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10% - 12%. Use of nucleosides with a longer half-life such as tenofovir plus emtricitabine has also been shown to decrease nevirapine resistance after single dose treatment. The findings may however differ in patients on chronic nevirapine treatment. An alternative strategy used by some experts is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time; however, no efficacy data supporting this have been reported. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than three weeks, some suggest that the PI-based regimen may need to be continued for up to four weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on etravirine and treatment interruption is lacking but its long half-life of approximately 40 hours suggest that stopping etravirine needs to be done carefully using the same suggestions for nevirapine and efavirenz for the time being.
- **Discontinuation and reintroduction of nevirapine**. Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a two-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than two weeks, nevirapine should be reintroduced with a dose escalation period of 200 mg once daily for 14 days followed by a 200 mg twice-daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B co-infection**. Patients with hepatitis B co-infection

(hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation. (See "Hepatitis B and HIV co-infection" section below.)

Considerations for Antiretroviral Use in Special Patient Populations

Acute HIV Infection

Panel's Recommendations

- Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time **(CIII)**.
- Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months **(CIII)**.
- If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels **(AIII)**.
- For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 cell count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection **(AII)**.
- If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. If therapy is deferred, genotypic resistance testing should still be considered, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.
- Since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug-resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available **(BIII)**.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report recent high-risk behavior. However, in some settings, patients may not always disclose or admit to high risk behaviors, or might not perceive their behaviors as high-risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test should be used in conjunction with an HIV antibody test to diagnose acute infection **(BII)**. Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL). A qualitative HIV RNA test can also be used in this setting. Patients diagnosed with acute HIV

infection on the basis of either a quantitative or a qualitative HIV RNA test should have confirmatory serologic testing performed at a subsequent time point **(AI)** (see Table 25 in the original guideline document).

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in 6% to 16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See "Utilization of Drug Resistance Testing in Clinical Practice" section in the original guideline document.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

See Potential Benefits and Harms sections in this summary for information on potential benefits and risks of treating acute HIV infection.

HIV-Infected Adolescents

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for antiretroviral therapy are usually appropriate for post pubertal adolescents because HIV-infected adolescents who were infected sexually or through injecting-drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not on the basis of age. Adolescents in early puberty (i.e., Tanner Stage I and II) should be administered doses using pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. Because puberty may be delayed in perinatally-HIV infected children, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than usual adult doses. Because data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt (i.e., Tanner Stage III in females and Tanner Stage IV in males) using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity.

Adherence Concerns in Adolescents

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health-care systems.

For a more detailed discussion on specific issues on therapy and adherence for HIV-infected adolescents see the National Guideline Clearinghouse (NGC) summary: Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection.

Special Considerations in Adolescent Females

Gynecological care is especially difficult to provide for the HIV infected female adolescent but is a critical part of their care. Because many adolescents with HIV infection are sexually active, contraception and prevention of HIV transmission should be discussed with the adolescent, including the interaction of specific antiretroviral drugs on birth control pills. The potential for pregnancy may also alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of child bearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring including periodic pregnancy testing and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see "HIV-Infected Women of Reproductive Age and Pregnant Women," below.

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need to support this appropriate transition in care for HIV-infected infants through adolescents.

Injection Drug Users (IDUs)

See the original guideline document for information about the challenges of treating IDUs infected with HIV, the efficacy of HIV treatment in IDUs, and IDU/HIV drug toxicities and interactions.

Provision of successful antiretroviral therapy for injection drug users is possible. It is enhanced by supportive clinical care sites and provision of drug treatment, awareness of interactions with methadone, and the increased risk of side effects and toxicities and the need for simple regimens to enhance medication adherence. These are important considerations in selection of regimens and providing appropriate patient monitoring in this population. Preference should be given to antiretroviral agents with lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and lack of interaction with methadone.

HIV-Infected Women of Reproductive Age and Pregnant Women

Panel's Recommendations

- When initiating antiretroviral therapy for women of reproductive age, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents **(AI)**.
- Efavirenz should be avoided for the woman who desires to become pregnant or who does not use effective and consistent contraception **(AIII)**.
- For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of viral suppression to <1,000 copies/mL to reduce the risk of transmission of HIV to the fetus and

newborn **(AI)**.
- Selection of an antiretroviral combination should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy **(AIII)**.
- Clinicians should consult the most current Public Health Services guidelines when designing a regimen for a pregnant patient **(AIII)**.

Women of Reproductive Age

In women of reproductive age, antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens should pregnancy occur. These regimens should be avoided in women who are trying to conceive or are not using effective and consistent contraception. Various PIs and NNRTIs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels (see Table 22 in the original guideline document). These changes may decrease the effectiveness of the oral contraceptives or potentially increase risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered. Amprenavir (and probably fosamprenavir) not only increases blood levels of both estrogen and progestin components, but oral contraceptives decrease amprenavir levels as well; these drugs should not be co-administered. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Counseling should be provided on an ongoing basis. Women who express a desire to become pregnant should be referred for pre-conception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy.

Pregnant Women

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of mother-to-child transmission (PMTCT) and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different from non-pregnant adults or adolescents.

PMTCT

Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT **(AI)**.

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussion with her clinician regarding the benefits versus risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy regardless of the infants' HIV status.

Regimen Considerations

See Table 26 in the original guideline document for short- and long-term effects of the antiretroviral drugs on the fetus and newborn. Based on available data, recommendations related to drug choices have been developed by the U.S. Public Health Service Task Force and can be found in Table 27 of the original guideline document.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the **Antiretroviral Pregnancy Registry (Telephone: 910-251-9087** or **1-800-258-4263**). The registry collects observational, non-experimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to the NGC summary: Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.

Lastly, the women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Post-Partum

Pregnant women who are started on antiretroviral therapy during therapy for the sole purpose of PMTCT and who do not meet criteria for starting treatment for their own health may choose to stop antiretroviral therapy after delivery. However, if therapy includes nevirapine, stopping all regimen components simultaneously may result in functional monotherapy because of its long half-life and subsequent increased risk for resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for PMTCT. In one study nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine. Further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens after delivery in situations where ongoing maternal treatment is not indicated.

Antiretroviral Considerations in Patients with Co-Infections

Hepatitis B (HBV)/HIV Coinfection

Treatment Recommendations for HBV/HIV Co-infected Patients

- All patients with HBV should be advised to abstain from alcohol; should receive hepatitis A vaccine, if found not to be immune at baseline (i.e., absence of hepatitis A total or IgG antibody); should be advised on methods to prevent HBV transmission (which do not differ from those to prevent HIV transmission); and should be evaluated for the severity of HBV infection.

- If neither HIV nor HBV infection requires treatment: Monitor the progression of both infections. If treatment becomes necessary for either infection, follow the guidelines listed in the scenarios below.
- If treatment is needed for HIV but not for HBV: The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will result in treatment of both infections. Because the preferred antiretroviral regimens all contain either lamivudine or emtricitabine, it is not possible to treat only HIV infection without using a nonpreferred regimen. To avoid development of HBV-resistant mutants, none of these agents should be used as the only agent with anti-HBV activity in an antiretroviral regimen.
- If treatment for HBV is needed: Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses: for example, tenofovir plus either emtricitabine or lamivudine. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with anti-HBV activity should be used in combination with lamivudine or emtricitabine for treatment of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression.
- Treating only HBV: In instances when HIV treatment is not an option or is not desirable, pegylated interferon-alpha may be used for the treatment of HBV infection, as it does not lead to emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10 mg dose; however, there is a theoretical risk for development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Because of the risk for HIV drug resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.
- Need to discontinue emtricitabine, lamivudine, or tenofovir: Monitor clinical course with frequent liver function tests, and consider the use of interferon, adefovir dipivoxil, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve.

Hepatitis C (HCV)/HIV Co-Infection

Assessment of HCV/HIV Co-Infection

Patients with HCV/HIV infection should be advised to avoid or limit alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if found to be susceptible. All patients with HCV, including those with HIV co-infection, should be evaluated for HCV therapy.

Standard indications for HCV therapy in the absence of HIV infection are detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. ALT levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HIV-associated liver disease. Liver biopsy is important for HCV therapeutic decision making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other comorbidities, probability of

adherence, and if there are contraindications to interferon-alpha, one of the drugs available for treatment of HCV.

Clinical trials in patients with HCV/HIV co-infection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60% to 70% for HCV genotype 2/3 but only 15% to 28% for genotype 1. These data are based on experience almost exclusively in carefully selected patients with CD4 counts over 200 cells/mm^3.

Treatment of HCV/HIV Co-Infection

Based on these observations, treatment of HCV is recommended according to standard guidelines with preference for those with higher CD4 counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible, but may be complicated by pill burden, drug toxicities, and drug interactions.

Scenarios for Treating HCV/HIV Co-Infection

Differences in HCV therapy management in the presence of HIV co-infection include:

- Ribavirin should not be given with didanosine because of the potential for drug-drug interactions leading to pancreatitis and lactic acidosis.
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important.
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible.
- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

Mycobacterium Tuberculosis Disease or Latent Tuberculosis Infection with HIV Coinfection

Panel's Recommendations

- The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection **(AI)**.
- Presence of active tuberculosis requires immediate initiation of treatment **(AI)**.
- The optimal timing of initiation of antiretroviral therapy in patients with active TB disease is not known. In antiretroviral-naïve patients, delay of antiretroviral therapy for 2 to 8 weeks after initiation of TB treatment may permit a better definition of causes of adverse drug reactions, and may reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS or a "paradoxical reaction") once antiretroviral therapy is initiated, but delay may increase the risk of HIV-related complications and mortality, particularly in those with very low CD4 cell counts **(BII)**.
- Directly observed therapy of TB treatment is strongly recommended for HIV-

infected patients with active TB disease **(AII)**.

- Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving antiretroviral therapy, with dosage adjustment as necessary **(AII)**.
- Where available, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with antiretroviral therapy **(AII)**.
- Rifampin/rifabutin-based regimens should be given at least three times weekly in HIV-infected patients with active disease and CD4 count <100 cells/mm^3; twice weekly is acceptable if CD4 count >100 cells/mm^3 **(AII)**.
- Once-weekly rifapentine is not recommended in the treatment of active TB disease in HIV-infected patients **(EI)**.
- The optimal management of IRIS is unknown; TB treatment and antiretroviral therapy should be continued, along with use of non-steroidal anti-inflammatory agents for milder cases and consideration of the use of high dose corticosteroids for 1 to 4 weeks in severe cases, with the length of treatment and taper based on control of symptoms **(BIII)**.
- Immune restoration as a result of antiretroviral therapy may be associated with conversion from a negative to a positive tuberculin skin test (TST) or IFN-gamma release assay (IGRA) in response to *M.TB*-specific proteins; repeat TST or IGRA is recommended in previously TST-negative or IGRA-negative individuals after initiation of antiretroviral therapy when the CD4 cell count exceeds 200 cells/mm^3 **(BII)**.
- HIV-infected individuals found to have latent TB infection (LTBI), defined as $\geq$5 mm skin test induration or positive IGRA with no prior treatment for LTBI and after appropriate evaluation to rule out active TB disease and no prior treatment of LTBI, should commence treatment with isoniazid (with pyridoxine) for 6 to 9 months **(AI)**.

Treatment of TB

Treatment of drug-susceptible TB disease in HIV-infected individuals should include the standard regimen outlined in treatment guidelines, which consist of isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given two months followed by INH + RIF for 4 to 7 months **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. A minimum of thrice weekly treatment with rifamycin-containing TB treatment regimens is recommended for patients with a CD4 cell count <100 cells/mm^3 **(AII)**. Once or twice weekly dosing has been associated with increased rates of development of rifamycin resistance in patients with advanced HIV, and once weekly rifapentine is not recommended **(E1)**.

Directly Observed Therapy (DOT)

DOT of TB treatment, in a manner supportive of the patients' needs is strongly recommended for patients with HIV/TB disease **(AII)**. In general, daily or thrice weekly DOT is recommended for the first two months and then three times weekly DOT for the continuation phase of 4 to 7 months **(BII)**.

Anti-TB/Antiretroviral Drug Toxicities and Interactions

All antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF, and PZA may also cause drug-induced hepatitis. These first line anti-tuberculous drugs should be used if at all possible even with coadministration of other hepatotoxic drug or baseline liver disease **(AIII)**. Patients receiving these drugs should have frequent monitoring for clinical symptoms of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Prevention Counseling for the HIV-Infected Patient

Prevention counseling is an essential component of management for HIV-infected persons. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of the following:

- Patient's knowledge and understanding of HIV transmission
- Patient's HIV transmission behaviors since the last encounter with a member of the health-care team

This should be followed by a discussion of strategies to prevent transmission that might be useful to the patient. Each member of the health care team can routinely provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued with the patient by the provider or by referral services.

Definitions:

Strength of the Evidence

Categories reflecting the quality of evidence supporting the recommendations:

I. At least one randomized trial with clinical results
II. Clinical trials with laboratory results
III. Expert opinion

Strength of Recommendation

A. Strong
B. Moderate
C. Optional
D. Should usually not be offered
E. Should never be offered

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

Recommendations are based upon expert opinion and scientific evidence. When appropriate data are not available, inconclusive, or contradictory, the recommendation is based on "expert opinion."

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall Benefits

The primary goals of antiretroviral therapy are to reduce human immunodeficiency virus (HIV)-related morbidity and prolong survival, improve quality of life, restore and preserve immunologic function, maximally and durably suppress viral load, and prevent vertical HIV transmission.

Specific Benefits

Potential Benefits of Early Therapy

- Maintenance of a higher CD4 count and prevention of potentially irreversible damage to the immune system
- Decreased risk for HIV-associated complications that can sometimes occur at CD4 counts >350 cells/mm^3, including tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, human papillomavirus (HPV)-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of nonopportunistic conditions, including cardiovascular disease, renal disease, liver disease, and non acquired immune deficiency syndrome (AIDS)-associated malignancies and infections
- Decreased risk of HIV transmission to others, which will have positive public health implications

Potential Benefits of Treating Acute Infection

Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of antiretroviral therapy.

POTENTIAL HARMS

Overall Harms

The risks of therapy for human immunodeficiency virus (HIV) infection include adverse effects on quality of life resulting from drug toxicities and dosing constraints; the potential, if therapy fails to effectively suppress viral replication, for the development of drug resistance, which may limit future treatment; and the potential need for continuing therapy indefinitely.

Specific Harms

Potential Risks of Early Therapy

- Development of treatment-related side effects and toxicities
- Development of drug resistance because of incomplete viral suppression, resulting in loss of future treatment options
- Less time for the patient to learn about HIV and its treatment and less time to prepare for the need for adherence to therapy
- Increased total time on medication, with greater chance of treatment fatigue
- Premature use of therapy before the development of more effective, less toxic, and/or better studied combinations of antiretroviral drugs
- Transmission of drug-resistant virus in patients who do not maintain full virologic suppression

Potential Risks of Treating Acute HIV Infection

The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

Refer to the original guideline document, including Tables 18 through 23, for important and more detailed information regarding the adverse effects associated with antiretroviral drugs, highly active antiretroviral therapy, and potential drug interactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

See Tables 21 to 23 in the original guideline document for drug combinations that should be avoided.

Some antiretroviral regimens or components are not recommended for human immunodeficiency virus type 1 (HIV-1) infected patients due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. See "What Not to Use" in the "Major Recommendations" field for detailed information.

- *Saquinavir mesylate* is contraindicated without ritonavir boosting because of poor bioavailability that averages only 4%, even with a concurrent high-fat meal.
- *Efavirenz* is contraindicated in the first trimester of pregnancy; avoid use in women with pregnancy potential.
- *Protease inhibitors (PIs)* are contraindicated with proton pump inhibitors.

- *Atazanavir (unboosted)* is contraindicated with proton pump inhibitors.
- *Tipranavir/ritonavir* is contraindicated in patients with moderate to severe (Child-Pugh class B & C) hepatic insufficiency.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Panel has carefully reviewed recent results from clinical trials in human immunodeficiency virus (HIV) therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.
- HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context is well known. Guidelines are only a starting point for medical decision-making. They can identify some of the boundaries of high care quality, but cannot substitute for sound judgment.
- These recommendations are not intended to supersede the judgment of clinicians who are knowledgeable in the care of human immunodeficiency virus (HIV)-infected individuals.
- Information included in these guidelines may not represent U.S. Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with FDA-defined legal standards for product approval.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Bethesda (MD): Department of Health and Human Services (DHHS); 2008 Jan 29. 128 p. [419 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Dec 1 (updated 2008 Jan 29)

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United States Government

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GUIDELINE STATUS

This is the current release of the guideline. It was last updated on January 29, 2008.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are summarized and highlighted on the AIDSinfo Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to aidsinfowebmaster@aidsinfo.nih.gov.

Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies of the guideline: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: www.cdcnpin.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Adherence to potent antiretroviral therapy. 2004 Oct 29. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available as a Personal Digital Assistant (PDA) download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number

(301)-562-1098. Web site: www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

The following is also available:

- Clinical management of the HIV-infected adult. A manual for midlevel clinicians. 1993 Sep (revised 2006). 399 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from Southeast AIDS Training and Education Center, Emory University School of Medicine, 735 Gatewood Road, NE, Atlanta, GA 30322. Telephone: (404) 727-2929; fax (404) 727-4562. E-mail: seatec@emory.edu. Web site: www.seatec.emory.edu.

The following Power Point slide sets based on the "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents" are also available:

- Comprehensive guideline summary. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Jan. 52 slides. Available from the AETC Web site.
- Initiation of therapy. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2009 Jan. 73 slides. Available from the AETC Web site.
- Managing the treatment-experienced patient. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Jan . 37 slides. Available from the AETC Web site.
- Special issues. Guidelines for the use of antiretroviral agents in adults and adolescents. AIDS Education and Training Center (AETC) National Resource Center. 2008 Jan. 57 slides. Available from the AETC Web site.

The following is also available:

- Antiretroviral Pocket Reference Cards. Antiretroviral therapy in adults and adolescents. AIDS Educational and Training Center (AETC) 2006 Dec. Available from the AETC Web site.
- A comprehensive Spanish-language Web site featuring information about HIV treatment and clinical trials is available at http://aidsinfo.nih.gov/infoSIDA/.

PATIENT RESOURCES

The following is available:

- HIV and its treatment: what you should know. Bethesda (MD): Department of Health and Human Services (DHHS); 2007 Oct. 15 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.
- Side effects of anti-HIV medications. Health information for patients. Bethesda (MD): Department of Health and Human Services (DHHS); 2005

Oct. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org.

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